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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/524,963	02/18/2005	David William Tonge	100815-1P US	3567

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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/524,963	TONGE ET AL.	
	Examiner	Art Unit	
	LESLIE A. ROYDS	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-50* is/are pending in the application.

4a) Of the above claim(s) *29,30,33-40 and 44-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-28,31-32,41-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *18Feb05; 15Jun05; 20Dec05; 08May06; 10May06; 09Nov06; 07Feb08; and 30Jan09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 26-50 are presented for examination.

Claims 1-25 were cancelled pursuant to the Preliminary Amendment dated February 18, 2005.

Acknowledgement is made of the present application as a National Stage (371) entry of PCT Application No. PCT/GB03/03653, filed August 20, 2003, and claims benefit under 35 U.S.C. 119(a-d) to U.K. Patent Application No. 0219660.8, filed August 23, 2002, of which a certified copy was filed February 18, 2005.

Applicant's Information Disclosure Statements (IDS) filed February 18, 2005 (one page); June 15, 2005 (five pages); December 20, 2005 (one page); May 8, 2006 (three pages); May 10, 2006 (one page); November 9, 2006 (two pages); February 7, 2008 (two pages); and January 30, 2009 (ten pages) have been received and entered into the present application. As reflected by the attached, completed copies of forms PTO-1449 and PTO/SB/08(a-b) (25 pages total), the Examiner has considered the cited references.

Requirement for Restriction/Election

Applicant's election of the invention of Group I (claims 26-28 and 31-43), directed to a method of treating cancer, reducing abnormal proliferation in a cancerous cell or inducing apoptosis in a cancerous cell comprising administering an effective amount of N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulphonamide, and the election of prostate cancer as the single disclosed specie of cancer for examination on the merits, in the reply filed March 18, 2009 is acknowledged by the Examiner. Because Applicant did not distinctly and specifically point out the supposed errors in the requirement, the election has been treated as an election **without traverse** (MPEP §818.03(a)).

Therefore, for the reasons above and those made of record at pages 2-7 of the previous Office

Action dated March 2, 2009, the requirement remains proper and is hereby made **FINAL**.

Claims 29-30, 33-40 and 44-50 are **withdrawn** from examination pursuant to 37 C.F.R. 1.142(b) as being directed to non-elected subject matter.

The claims corresponding to the elected subject matter are claims 26-28, 31-32 and 41-43 and such claims are herein acted on the merits.

Information Disclosure Statement filed February 18, 2005

The information disclosure statement filed February 18, 2005 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

Objection to the Oath/Declaration

The oath or declaration filed February 18, 2005 is defective because the declaration contains handwritten changes to the name of each inventor that have not been initialed or dated by the individual(s) who executed the declaration. A new oath or declaration in compliance with 37 C.F.R. 1.67(a) identifying this application by serial number and filing date is required. Please reference MPEP §§602.01 and 602.02.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 26-28, 31-32 and 41-43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claims 26, 27 and 28 recite the broad recitation "a warm blooded animal", but then recite “such as man”, which is a narrower statement of the limitation. The phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. Clarification is requested.

For these reasons, the claims fail to meet the tenor and express requirements of 35 U.S.C. 112, second paragraph, and are, thus, properly rejected.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 26-28, 31-32 and 41-43 are rejected under 35 U.S.C. 102(b) as being anticipated by Bradbury et al. (U.S. Patent No. 5,866,568; 1999).

Bradbury et al. teaches heterocyclic compounds that possess endothelin receptor antagonist activity and are useful for the treatment of diseases or medical conditions in which elevated or abnormal levels of endothelin play a significant causative role (abstract). Bradbury et al. teaches that compounds of particular interest include various exemplified embodiments, such as, *inter alia*, the compound of Example 36 (col.11, l.3-10), i.e., N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulphonamide (col.41, Ex.36). Bradbury et al. further discloses that the compounds are administered for therapeutic purposes to warm-blooded animals, including man, requiring such treatment in the form of a pharmaceutical composition (col.17, l.19-23), wherein the compound is administered such that a daily oral dose of up to 50 mg/kg body weight or a daily parenteral dose of up to 5 mg/kg body weight is received and given in divided doses, if necessary (i.e., an "effective amount" as recited in instant claims 26-28; col.17, l.50-61) and various diseases that may be treated include, *inter alia*, hypertension, chronic renal failure, certain cancers, etc. (col.14, l.62-col.15, l.10).

Though it is noted that Bradbury et al. does not specifically teach the instantly claimed objective of treating prostate cancer (claim 26), reducing abnormal proliferation or inducing differentiation of a cancerous cell (claim 27) or inducing apoptosis in a cancer cell (claim 28), the preamble objectives of (1) treating cancer as in instant claim 26 (i.e., prostate cancer, which is the elected species under examination), (2) reducing abnormal proliferation or inducing differentiation in a cancerous cell as in instant claim 27, or (3) inducing apoptosis in a cancerous cell as in instant claim 28 fail to patentably limit the instant claims because the body of the claim(s) clearly sets forth all of the limitations of the instantly claimed invention (i.e., administering an effective amount of N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulphonamide) and the preamble simply states the purpose of the instant method(s). See MPEP §2111.02(II), which states, "If the body of a claim fully and intrinsically

sets forth all of the limitations of the claimed invention, and the preamble merely states, for example, the purpose or intended use of the invention, rather than any distinct definition of any of the claimed invention's limitations, then the preamble is not considered a limitation and is of no significance to claim construction. *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305, 51 USPQ2d 1161, 1165 (Fed. Cir. 1999). See also *Rowe v. Dror*, 112 F.3d 473, 478, 42 USPQ2d 1550, 1553 (Fed. Cir. 1997) ("where a patentee defines a structurally complete invention in the claim body and uses the preamble only to state a purpose or intended use for the invention, the preamble is not a claim limitation").

In the instant case, because the body of the claim sets forth all of the limitations of the claimed invention and the preambles are merely directed to the purpose of the claimed method (i.e., "treating cancer" or "reducing abnormal proliferation in a cancerous cell" or "inducing apoptosis in a cancerous cell"), the preambles do not patentably limit the instant claims. Moreover, with regard to the instant limitations of present claims 41-43 that further define the type of prostate cancer being treated (i.e., that it is either metastatic as in claim 41, non-metastatic as in claim 42 or producing bone metastases as in claim 43), since the preamble objective of treating prostate cancer does not patentably limit the claims, these limitations of instant claims 41-43 also do not patentably limit the claims because the claims are directed to further limitations of the cancer to be treated. Therefore, since Bradbury et al. clearly teaches each and every defining step and limitation of the instant claims, the fact that Bradbury et al. does not explicitly teach the purpose of the instantly claimed method (or dependent limitations thereof, such as those of instant claims 41-43 that further define the cancer of the preamble to be treated) is immaterial because the preamble limitations do not result in a manipulative difference in the presently claimed process(es) and, thus, do not serve to the limit the instantly claimed invention. Compare to *Jansen v. Rexall Sundown, Inc.*, 342 F.3d 1329, 1333-34, 68 USPQ2d 1154, 1158 (Fed. Cir. 2003), which is directed to a situation where the method preamble did serve to patentably limit the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 26-28, 31-32 and 41-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bradbury et al. (U.S. Patent No. 5,866,568; 1999) in view of Hsu et al. ("ET-1 Expression and Growth Inhibition of Prostate Cancer Cells: A Retinoid Target with Novel Specificity", *Cancer Research*, 1998; 58:4817-4822) and Nelson et al. ("Identification of Endothelin-1 in the Pathophysiology of Metastatic Adenocarcinoma of the Prostate", *Nature Medicine*, 1995; 1(9):944-949, cited by Applicant).

Bradbury et al. teaches heterocyclic compounds that possess endothelin receptor antagonist activity and are useful for the treatment of diseases or medical conditions in which elevated or abnormal levels of endothelin play a significant causative role (abstract). Bradbury et al. teaches that compounds of particular interest include various exemplified embodiments, such as, *inter alia*, the compound of Example 36 (col.11, l.3-10), i.e., N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulphonamide (col.41, Ex.36). Bradbury et al. further discloses that the compounds are administered for therapeutic purposes to warm-blooded animals, including man, requiring such

treatment in the form of a pharmaceutical composition (col.17, l.19-23), wherein the compound is administered such that a daily oral dose of up to 50 mg/kg body weight or a daily parenteral dose of up to 5 mg/kg body weight is received and given in divided doses, if necessary (i.e., an "effective amount" as recited in instant claims 26-28; col.17, l.50-61) and various diseases that may be treated include, *inter alia*, hypertension, chronic renal failure, certain cancers (understood to include both non-metastatic and metastatic), etc. (col.14, l.62-col.15, l.10). Bradbury et al. demonstrates that the compounds of the disclosure show inhibition of endothelin-1 (i.e., function as an endothelin-1 receptor antagonist by inhibiting binding of endothelin-1 to its receptors) (col.15, l.14-64).

Bradbury et al. fails to specifically teach the treatment of prostate cancer (claims 26 and 31-32), either metastatic (claim 41) or non-metastatic (claim 42), that the cancer is producing bone metastases (claim 43) or that the disclosed compound is effective for reducing abnormal proliferation in a cancerous cell or inducing differentiation of a cancerous cell (claim 27) or inducing apoptosis in a cancerous cell (claim 28).

Hsu et al. teaches that endothelin-1 (ET-1) is a potent vasoconstrictor and an important growth stimulator in various cancers, including prostate cancer, which suggests that blockage of ET-1 production is capable of suppressing tumor growth and metastasis (abstract). Hsu et al. teaches that a 2.6 times higher level of ET-1 was found in the plasma of patients with advanced prostate cancer as compared with healthy males, which suggests that ET-1 regulates and promotes prostate tumor growth (col.1, para.2, p.4817).

Nelson et al. teaches that advanced, hormone-refractory prostate cancer is characterized by painful osteoblastic bone metastases (abstract). Nelson et al. discloses that endothelin-1 (ET-1) is a normal ejaculate protein that also stimulate osteoblasts and teaches that the ectopic secretion of ET-1 may be a mediator of the osteoblastic response of bone to metastatic prostate cancer (abstract) because osteoblasts have high-affinity ET-1 receptors, act on a number of pathways and inhibit bone resorption

and motility of osteoclasts, which enhances the emergence of osteoblastic lesions (col.1-2, p.947). Nelson et al. states that ET-1 may have a significant role in the formation of osteosclerotic bone lesions and suggests that, for endothelin-secreting phenotypes of advanced prostate cancer, the use of therapies directed against endothelin is both rational and strategic (col.2, para.2-3, p.947).

One of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious to particularly treat prostate cancer (either non-metastatic or metastatic) or to reduce the abnormal proliferation of prostate cancer cells using the compound and composition thereof of Bradbury et al. because (1) Bradbury et al. teaches that the compound N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulphonamide functions as an endothelin-1 receptor antagonist via inhibiting binding of ET-1 to its receptors and is useful for treating diseases or medical conditions in which elevated or abnormal levels of endothelin play a significant causative role, including certain cancers and (2) Hsu et al. teaches that ET-1 is an important growth stimulator that both regulates and promotes tumor growth in prostate cancer and that blockage of ET-1 is capable of suppressing both tumor growth (such as, e.g., tumors in a non-metastatic state) and tumor metastasis (i.e., tumors in a metastatic state). Such a person would have been motivated to do so because the N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]-phenyl)-pyridine-3-sulphonamide compound of Bradbury et al. functions as an inhibitor of ET-1 and, as evidenced by Hsu et al., ET-1 is known to regulate and promote prostate tumor growth and metastasis. Thus, the skilled artisan would have had a reasonable expectation of successfully treating prostate cancer or reducing abnormal proliferation of prostate cancer cells using this same compound of Bradbury et al. because said compound was known in the prior art as an ET-1 inhibitor and useful for treating cancers and ET-1 was known to promote the growth and metastasis of prostate tumors.

Furthermore, one of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious to use the N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]-phenyl)-

pyridine-3-sulphonamide compound of Bradbury et al. to treat prostate cancer that is also producing bone metastases because (1) Bradbury et al. teaches that the compound N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulphonamide functions as an ET-1 receptor antagonist via inhibiting binding of ET-1 to its receptors and is useful for treating diseases or medical conditions in which elevated or abnormal levels of endothelin play a significant causative role, including certain cancers and (2) ET-1 is not only a potent stimulator of tumor growth and metastasis in prostate cancer (as evidenced by Hsu et al.), but is also a stimulator of osteoblasts and is known to contribute to the osteoblastic response of bone to metastatic prostate cancer to form painful osteoblastic bone metastases, as evidenced by Nelson et al. Such a person would have been motivated to do so not only to inhibit the function of ET-1 in promoting both prostate tumor growth and metastases, but also to inhibit the function of ET-1 in stimulating osteoblasts that form painful osteoblastic bone metastases in advanced stages of prostate cancer.

Though the effects in inducing differentiation or apoptosis in a cancerous cell, wherein the cancerous cell is a prostate cancer cell (claims 27-28) are not explicitly noted in the combination of cited references, it is noted that the teachings of the identical manner of administration of the identical compound to that presently claimed in the same host in a therapeutically effective amount for treating the identical disorder as described above from the prior art must necessarily possess such differentiation-inducing or apoptosis-inducing effects, even though such properties may not have been appreciated by the patentee(s) at the time of the invention. Products of identical chemical composition cannot exert mutually exclusive properties when administered under the same circumstances or, in the present case, the same host in the same amount. Please see MPEP §2112.

In re Best (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter, which there is reason to believe includes functions and/or properties that are newly cited, or is identical to a product instantly claimed. In such a situation the

burden is shifted to the Applicants to "prove that subject matter to be shown in the prior art does not possess the characteristic relied on" (205 USPQ 594, second column, first full paragraph). There is no requirement that a person of ordinary skill in the art would have recognized the newly cited function and/or property at the time of invention, so long as the function and/or property can be demonstrated to be reasonably expected to be present. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003); see also *Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1320, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004) ("[T]he fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention"). Note that, even though *Toro* was decided in the context of inherent anticipation, considerations of inherent teachings arise both in the context of anticipation and obviousness (see, e.g., *In re Napier*, 55 F.3d 610, 613, 34 USPQ2d 1782, 1784 (Fed. Cir. 1995) or *In re Grasselli*, 713 F.2d 731, 739, 218 USPQ 769, 775 (Fed. Cir. 1983) and MPEP §2112).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 26-28, 31-32 and 41-43 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 42-44 of U.S. Patent Application No. 11/720,001.

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claims because the examined claims are either anticipated by, or would have been obvious over, the reference claims.

Although the conflicting claims are not identical, the claims of the instant patent application and those of the cited application are not considered patentably distinct from each other because the pending claims are anticipated and/or rendered obvious by the copending claims.

The copending claims clearly provide for the treatment of cancer, specifically prostate cancer, in a warm-blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a combination of N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulphonamide and an anti-mitotic cytotoxic agent (copending claims 42-44).

Though it is noted that the copending claims do not specifically teach the instantly claimed objective of reducing abnormal proliferation or inducing differentiation of a cancerous cell (claim 27) or inducing apoptosis in a cancer cell (claim 28), the preamble objectives of (1) reducing abnormal proliferation or inducing differentiation in a cancerous cell as in instant claim 27, or (2) inducing apoptosis in a cancerous cell as in instant claim 28 fail to patentably limit the instant claims because the body of the claim(s) clearly sets forth all of the limitations of the instantly claimed invention (i.e., administering an effective amount of N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulphonamide) and the preamble simply states the purpose of the instant method(s). See MPEP §2111.02(II), which states, "If the body of a claim fully and intrinsically sets forth all of the limitations of the claimed invention, and the preamble merely states, for example, the purpose or intended use of the invention, rather than any distinct definition of any of the claimed invention's limitations, then the preamble is not considered a limitation and is of no significance to claim construction. *Pitney Bowes,*

Inc. v. Hewlett-Packard Co., 182 F.3d 1298, 1305, 51 USPQ2d 1161, 1165 (Fed. Cir. 1999). See also *Rowe v. Dror*, 112 F.3d 473, 478, 42 USPQ2d 1550, 1553 (Fed. Cir. 1997) ("where a patentee defines a structurally complete invention in the claim body and uses the preamble only to state a purpose or intended use for the invention, the preamble is not a claim limitation").

In the instant case, because the body of the claim sets forth all of the limitations of the claimed invention and the preambles are merely directed to the purpose of the claimed method (i.e., "treating cancer" or "reducing abnormal proliferation in a cancerous cell" or "inducing apoptosis in a cancerous cell"), the preambles do not patentably limit the instant claims. Moreover, with regard to the instant limitations of present claims 41-43 that further define the type of prostate cancer being treated (i.e., that it is either metastatic as in claim 41, non-metastatic as in claim 42 or producing bone metastases as in claim 43), since the preamble objective of treating prostate cancer does not patentably limit the claims, these limitations of instant claims 41-43 also do not patentably limit the claims because the claims are directed to further limitations of the cancer to be treated. Therefore, since the copending claims clearly teach each and every defining step and limitation of the instant claims, the fact that the copending claims do not explicitly teach the purpose of the instantly claimed method (or dependent limitations thereof, such as those of instant claims 41-43 that further define the cancer of the preamble to be treated) is immaterial because the preamble limitations do not result in a manipulative difference in the presently claimed process(es) and, thus, do not serve to the limit the instantly claimed invention, absent factual evidence to the contrary.

Accordingly, rejection of claims 26-28, 31-32 and 41-43 is proper over claims 42-44 of U.S. Patent Application No. 11/720,001 as claiming obvious and unpatentable variants thereof.

Claims 26-28, 31-32 and 41-43 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 42-44 of U.S. Patent Application

No. 11/720,001 in view of Bradbury et al. (U.S. Patent No. 5,866,568; 1999), Hsu et al. ("ET-1 Expression and Growth Inhibition of Prostate Cancer Cells: A Retinoid Target with Novel Specificity", *Cancer Research*, 1998; 58:4817-4822) and Nelson et al. ("Identification of Endothelin-1 in the Pathophysiology of Metastatic Adenocarcinoma of the Prostate", *Nature Medicine*, 1995; 1(9):944-949).

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claims because the examined claims are either anticipated by, or would have been obvious over, the reference claims.

Although the conflicting claims are not identical, the claims of the instant patent application and those of the cited application are not considered patentably distinct from each other because the pending claims are anticipated and/or rendered obvious by the copending claims.

The copending claims clearly provide for the treatment of cancer, specifically prostate cancer, in a warm-blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a combination of N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulphonamide and an anti-mitotic cytotoxic agent (copending claims 42-44).

The copending claims fail to teach the treatment of either metastatic (claim 41) or non-metastatic prostate cancer (claim 42), that the cancer is producing bone metastases (claim 43) or that the disclosed compound is effective for inducing differentiation of a cancerous cell (claim 27) or inducing apoptosis in a cancerous cell (claim 28).

Bradbury et al. teaches heterocyclic compounds that possess endothelin receptor antagonist activity and are useful for the treatment of diseases or medical conditions in which elevated or abnormal levels of endothelin play a significant causative role (abstract). Bradbury et al. teaches that compounds of particular interest include various exemplified embodiments, such as, *inter alia*, the compound of

Example 36 (col.11, l.3-10), i.e., N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulphonamide (col.41, Ex.36) and further demonstrates that the compounds of the disclosure show inhibition of endothelin-1 (i.e., function as an endothelin-1 receptor antagonist by inhibiting binding of endothelin-1 to its receptors) (col.15, l.14-64).

Hsu et al. teaches that endothelin-1 is a potent vasoconstrictor and an important growth stimulator in various cancers, including prostate cancer, which suggests that blockage of ET-1 production is capable of suppressing tumor growth and metastasis (abstract). Hsu et al. teaches that a 2.6 times higher level of ET-1 was found in the plasma of patients with advanced prostate cancer as compared with healthy males, which suggests that ET-1 regulates and promotes prostate tumor growth (col.1, para.2, p.4817).

Nelson et al. teaches that advanced, hormone-refractory prostate cancer is characterized by painful osteoblastic bone metastases (abstract). Nelson et al. discloses that endothelin-1 (ET-1) is a normal ejaculate protein that also stimulate osteoblasts and teaches that the ectopic secretion of ET-1 may be a mediator of the osteoblastic response of bone to metastatic prostate cancer (abstract) because osteoblasts have high-affinity ET-1 receptors, acts on a number of pathways and inhibits bone resorption and motility of osteoclasts, which enhances the emergence of osteoblastic lesions (col.1-2, p.947). Nelson et al. states that ET-1 may have a significant role in the formation of osteosclerotic bone lesions and suggests that, for endothelin-secreting phenotypes of advanced prostate cancer, the use of therapies directed against endothelin is both rational and strategic (col.2, para.2-3, p.947).

One of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious to treat non-metastatic or metastatic prostate cancer or to reduce the abnormal proliferation of prostate cancer cells using the copending composition because (1) Bradbury et al. teaches that the compound N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]-phenyl)-pyridine-3-sulphonamide functions as an ET-1 receptor antagonist via inhibiting binding of ET-1 to its receptors and is useful for treating diseases or medical conditions in which elevated or abnormal levels of endothelin

play a significant causative role, including certain cancers and (2) Hsu et al. teaches that ET-1 is an important growth stimulator that both regulates and promotes tumor growth in prostate cancer and that blockage of ET-1 is capable of suppressing both tumor growth (such as, e.g., tumors in a non-metastatic state) and tumor metastasis (i.e., tumors in a metastatic state). Such a person would have been motivated to do so because the N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]-phenyl)-pyridine-3-sulphonamide compound of the copending claims functions as an inhibitor of ET-1 as evidenced by Bradbury et al. and, as evidenced by Hsu et al., ET-1 is known to regulate and promote prostate tumor growth and metastasis. Thus, the skilled artisan would have had a reasonable expectation of successfully treating non-metastatic or metastatic prostate cancer using the composition of the copending claims because the sulphonamide compound of the copending composition was known in the prior art as an ET-1 inhibitor and ET-1 was known to promote the growth and metastasis of prostate tumors.

Furthermore, one of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious to use the copending composition to treat prostate cancer that is also producing bone metastases because (1) Bradbury et al. teaches that the compound N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulphonamide functions as an ET-1 receptor antagonist via inhibiting binding of ET-1 to its receptors and is useful for treating diseases or medical conditions in which elevated or abnormal levels of endothelin play a significant causative role, including certain cancers and (2) ET-1 is not only a potent stimulator of tumor growth and metastasis in prostate cancer (as evidenced by Hsu et al.), but is also a stimulator of osteoblasts and is known to contribute to the osteoblastic response of bone to metastatic prostate cancer to form painful osteoblastic bone metastases, as evidenced by Nelson et al. Such a person would have been motivated to do so not only to inhibit the function of ET-1 in promoting both prostate tumor growth and metastases, but also to inhibit the function of ET-1 in stimulating osteoblasts that form painful osteoblastic bone metastases in advanced stages of prostate cancer.

Though the effects in inducing differentiation or apoptosis in a cancerous cell, wherein the cancerous cell is a prostate cancer cell (claims 27-28) are not explicitly noted in the copending claims, it is noted that the teaching of the identical manner of administration of the identical compound to that presently claimed in the same host in a therapeutically effective amount for treating the identical disorder must necessarily possess such differentiation-inducing or apoptosis-inducing effects, even though such properties may not have been appreciated by the patentee(s) at the time of the invention. Products of identical chemical composition cannot exert mutually exclusive properties when administered under the same circumstances or, in the present case, the same host in the same amount. Please see MPEP §2112.

In re Best (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter, which there is reason to believe includes functions and/or properties that are newly cited, or is identical to a product instantly claimed. In such a situation the burden is shifted to the Applicants to "prove that subject matter to be shown in the prior art does not possess the characteristic relied on" (205 USPQ 594, second column, first full paragraph). There is no requirement that a person of ordinary skill in the art would have recognized the newly cited function and/or property at the time of invention, so long as the function and/or property can be demonstrated to be reasonably expected to be present. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003); see also *Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1320, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004) ("[T]he fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention"). Note that, even though *Toro* was decided in the context of inherent anticipation, considerations of inherent teachings arise both in the context of anticipation and obviousness (see, e.g., *In re Napier*, 55 F.3d 610, 613, 34 USPQ2d 1782, 1784 (Fed. Cir. 1995) or *In re Grasselli*, 713 F.2d 731, 739, 218 USPQ 769, 775 (Fed. Cir. 1983) and MPEP §2112).

Accordingly, rejection of claims 26-28, 31-32 and 41-43 is proper over claims 42-44 of U.S. Patent Application No. 11/720,001 as claiming obvious and unpatentable variants thereof.

Conclusion

Rejection of claims 26-28, 31-32 and 41-43 is proper.

Claims 29-30, 33-40 and 44-50 are **withdrawn** from consideration pursuant to 37 C.F.R. 1.142(b).

No claims of the present application are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LESLIE A. ROYDS whose telephone number is (571)-272-6096. The examiner can normally be reached on Monday-Friday (9:00 AM-5:30 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571)-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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